PATENT SPECIFICATION (11) 1 571 433

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(21) Application No. 39954/77 (22) Filed 16 Feb. 1977
(62) Divided out of No. 1571432
(31) Convention Application No. 2606635
(32) Filed 19 Feb. 1976 in
(33) Federal Republic of Germany (DE)
(44) Complete Specification published 16 July 1980
(51) INT CL³ C07C 69/63 69/716 121/407
(52) Index at acceptance
C2C 20Y 304 313 31Y 326 339 351 355 366 368 376 37X 387 440 625 628 62Y 638 AA CH MC UV

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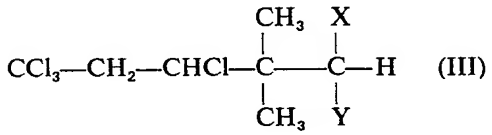
(54) NOVEL CHLORINE-SUBSTITUTED DICARBOXYLIC ACID DERIVATIVES

(71) We, BAYER AKTIENGESELLSCHAFT, a body corporate, organised under the laws of Germany, of Leverkusen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

The present invention relates to certain chlorine-substituted dicarboxylic acid derivatives and to a process for their preparation.

In particular, the present invention provides, as new compounds, the 1,1 - dimethyl - 2,4,4,4 - tetrachlorobutyl - malonic acid derivatives of the general formula



(III)

in which

X and Y, which may be identical or different, each represent CN, the radical —COOR or the radical —COR¹, provided that X and Y do not both represent CN,

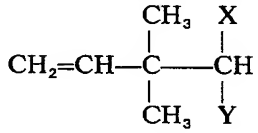
R represents C_1—C_4 alkyl, aralkyl or aryl, and

R¹ represents C_1—C_4 alkyl.

Preferred compounds of the formula (III) are those in which X and Y, which may be identical or different, each represent CN, acetyl (—$COCH_3$) or the radical —COOR in which R represents C_{1-4}-alkyl, benzyl or phenyl.

Compounds in which X and Y represent an alkoxycarbonyl group —COOR, in which R represents methyl, ethyl or tert.-butyl, are particularly preferred.

The present invention also provides a process for the preparation of a compound of the formula (III) in which a 1,1 - dimethyl - 2 - propenyl - malonic acid derivative of the general formula



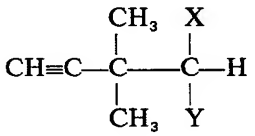
(IV)

in which

X and Y have the above-mentioned meanings, is reacted with CCl_4 in the presence of a diluent (which term includes a solvent) and of a suitable catalyst.

The compounds of the formula (IV) are the subject of copending U.K. Patent Application No. 39955/77 (Serial No. 1,571,434). Such a compound can be obtained by

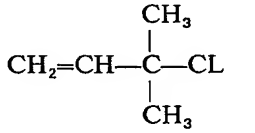
(a) hydrogenating a dimethylpropynyl - malonic acid derivative of the general formula



(V)

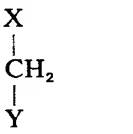
in which

X and Y have the above-mentioned meanings, in the presence of a Lindlar catalyst, or by (b) reacting 3 - methyl - 3 - chloro - but - 1 - ene of the formula



(VI)

with a compound of the general formula



(VII)

in which

X and Y have the above-mentioned meanings, in the presence of a basic catalyst and/or a diluent.

3 - Methyl - 3 - chloro - but - 1 - ene is known (see J. Chem. Soc. London 1948, page 530).

The compounds of the formula (VII) are known or can be prepared analogously to known processes.

The compounds of the formula (V) are known or can be prepared analogously to known processes (see J. Biol. Chem., volume 175, page 771; 1948).

The compounds of the formula (IV) are obtained from the starting materials of the formula (V) by a reaction which is in itself known, that is to say the partial reduction of alkynes with hydrogen in the presence of so-called Lindlar catalysts, or by reacting 3 - methyl - 3 - chloro - but - 1 - ene with compounds of the formula (VII) in the presence of basic agents.

Basic agents which can be used are, for example, alkali metal hydroxides, such as NaOH or KOH, carbonates, such as Na_2CO_3 or K_2CO_3, or, preferably, alcoholates, such as sodium methylate, sodium ethylate, sodium isopropylate or potassium tert.-butylate. In the latter case, the solvents used are preferably alcohols, such as methanol, ethanol, isopropanol or butanol.

Other solvents which can be used are: hydrocarbons, such as pentane, hexane or toluene, ethers, such as tetrahydrofuran, dioxan, diisopropyl ether or glycol dimethyl ether, or ketones, such as acetone or butanone.

The reaction is carried out at temperatures between 0° and 150°C, and preferably between 20° and 100°C.

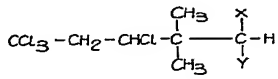
Compounds of the formula (III) are prepared by an addition reaction of carbon tetrachloride with compounds of the formula (IV).

An addition reaction of carbon tetrachloride with olefins is known. It is catalysed by compounds which form free radicals, such as, for example, peroxides, azo compounds, transition metal complexes or catalyst systems which contain copper(I) salts and a base, for example piperidine.

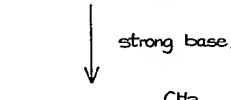
The addition reaction is preferably carried out in the presence of a peroxide, such as, for example, di - tert. - butyl peroxide or benzoyl peroxide, or of an azo compound, such as, for example, azo - bis - isobutyronitrile; benzoyl peroxide is particularly preferred.

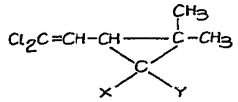
The reaction is usually carried out using an excess of carbon tetrachloride as the solvent and under normal pressure or elevated pressure. The usual temperature range accordingly extends from 77° up to 150°C. However, the reaction can also be carried out in other inert organic solvents.

The compounds of the formula (III) may be employed in the preparation of 2,2 - dimethyl - 3 - (2',2' - dichlorovinyl) - cyclopropane - 1 - carboxylic acid, according to the following reaction sequence:

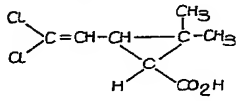


(III)





(II)



(I).

The conversion of the compounds (II) into the compound (I) is effected, depending upon the particular meanings of X and Y, by (a) complete or partial saponification and subsequent decarboxylation, (b) elimination of an alkylcarbonyl (—COR^1) group and saponification or (c) elimination of an acetyl radical and oxidation of the resulting ketone.

The compounds of the formula (II), their preparation and their conversion, by the above methods, into 2,2 - dimethyl - 3 - (2',2' - dichlorovinyl) - cyclopropane - 1 - carboxylic acid are disclosed and claimed in copending U.K. Patent Application No. 6465/77 (Serial No. 1,571,432).

The process of the present invention and methods of preparing appropriate starting material are illustrated by the following Examples.

Example 1

113 g of dimethylpropynyl - malonic acid diethyl ester were dissolved in 500 ml of petroleum ether in a hydrogenation autoclave with a glass insert. 10 g of a Lindlar catalyst (5% Pd on $CaCO_3$) were added and the hydrogenation was carried out at 70°C until the theoretically calculated amount of hydrogen had been

taken up. The mixture was then allowed to cool, the catalyst was filtered off and the solvent was stripped off under reduced pressure. 108 g of a very slightly yellowish coloured liquid remained and according to analysis by gas chromatography this consisted to the extent of 90% of 1,1 - dimethyl - 2 - propenylmalonic acid diethyl ester. Yield: 86% of theory. The nuclear magnetic resonance spectrum confirmed the structure: δ (in $CDCl_3$): 1.2 ppm (singlet+triplet, 12 protons); 3.3 ppm (singlet, 1 proton); 4.15 ppm (quartet, 4 protons); and 4.95 ppm and 6 ppm (multiplet; 2+1 protons).

Example 2

250 g of crude 1,1 - dimethyl - 2 - propenyl - malonic acid diethyl ester (approximately 90% pure) were dissolved in 2,000 ml of dry carbon tetrachloride and 40 g of benzoyl peroxide were added. The mixture was boiled for 8 hours under reflux, 20 g of benzoyl peroxide were added and the mixture was boiled for a further 8 hours. After cooling, the mixture was washed with cold dilute sodium hydroxide solution in order to remove the benzoic acid formed and the organic phase was dried with sodium sulphate and filtered and the solvent was distilled off under reduced pressure. The residue was subjected to fractional distillation under a high vacuum. 277 g of 1,1 - dimethyl - 2,4,4,4 - tetra - chlorobutyl - malonic acid diethyl ester with a boiling point of 132—138°C/0.2 mm Hg were obtained. Yield: 73% of theory. The nuclear magnetic resonance spectrum confirmed the structure. δ (in $CDCl_3$): 1.35 ppm (multiplet, 12 protons); 3.2 ppm (multiplet, 2 protons); 3.9 ppm (singlet, 1 proton); 4.25 ppm (quartet, 4 protons); and 4.8 ppm (multiplet, 1 proton).

Example 3

23 g of sodium were dissolved in 500 ml of absolute ethanol, 176 g of malonic acid diethyl ester were added dropwise, 1 g of hydroquinone was added and 104.5 g of 3 - chloro - 3 - methyl - 1 - butene (prepared according to J. Chem. Soc. London *1948*, page 530) were then added dropwise at 60—70°C. When the dropwise addition was complete, the mixture was heated to the reflux temperature for a further one hour. It was then allowed to cool and left to stand overnight. After filtering, the sodium chloride which had been filtered off was rinsed with ethanol and the combined filtrates were concentrated *in vacuo*. The residue was rendered acid with ice-cold dilute hydrochloric acid and extracted three times with methylene chloride. The methylene chloride extracts were washed with sodium carbonate solution and then with water, the organic phase was dried over sodium sulphate, the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was subjected to fractional distillation. 161 g of a liquid which had a boiling point of 76—82°C/0.2 mm Hg were obtained. As was found by analysis by gas chromatography, the product was identical with the 1,1 - dimethyl - 2 - propenyl - malonic acid diethyl ester obtained in Example 1.

Example 4

23 g of sodium were dissolved in 500 ml of absolute ethanol, 124 g of cyanoacetic acid ethyl ester were added dropwise and 102.5 g of 3 - chloro - 3 - methyl - 1 - butyne (prepared according to J. Am. Chem. Soc. *79*, 2,142; 1957) were then added dropwise at 60—70°C. When the dropwise addition was complete, the mixture was heated to the reflux temperature for a further one hour. After cooling, it was evaporated in a rotary evaporator and the residue was rendered acid with ice-cold dilute hydrochloric acid and extracted three times with methylene chloride. The methylene chloride extracts were washed with sodium carbonate solution and then with water and the organic phase was dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue was subjected to fractional distillation under a high vacuum. 1,1 - Dimethyl - 2 - propynyl - cyanoacetic acid ethyl ester boiled at a boiling point of 92—98°C/0.5 mm Hg. The nuclear magnetic resonance spectrum confirmed the structure:

δ (in $CDCl_3$): 1.3 ppm (triplet, 3 protons); 1.5 ppm (singlet, 6 protons); 2.4 ppm (singlet, 1 proton); 3.6 ppm (singlet, 1 proton) and 4.3 ppm (quartet, 2 protons).

Example 5

89.5 g of 1,1 - dimethyl - 2 - propynyl - cyanoacetic acid ethyl ester were dissolved in 500 ml of petroleum ether in a hydrogenation autoclave with a glass insert, 10 g of Lindlar catalyst (5% Pd on $CaCO_3$) were added and the hydrogenation was carried out at 60—80°C until the theoretically calculated amount of hydrogen had been taken up. After cooling, the catalyst was filtered off and the solvent was removed under reduced pressure. 81 g of a yellow oil which consisted mainly of 1,1 - dimethyl - 2 - propenyl - cyanoacetic acid ethyl ester remained and this was employed direct in the next stage (see Example 6).

Example 6

81 g of crude 1,1 - dimethyl - 2 - propenyl - cyanoacetic acid ethyl ester

were dissolved in 750 ml of carbon tetrachloride, 40 g of benzoyl peroxide were added and the mixture was boiled under reflux for 24 hours. After cooling, it was washed with cold dilute sodium hydroxide solution in order to remove the benzoic acid formed, the organic phase was dried with sodium sulphate and, after the sodium sulphate had been filtered off, the solvent was distilled off. The residue was subjected to fractional distillation under a high vacuum. 92 g of 1,1 - dimethyl - 2,4,4,4 - tetra - chlorobutyl - cyanoacetic acid ethyl ester with a boiling point of 122—130°C/0.1 mm Hg were obtained.

The nuclear magnetic resonance spectrum confirmed the structure:

δ (in $CDCl_3$): 1.25 ppm (multiplet, 9 protons); 3.2 ppm (multiplet, 2 protons); 4.2 ppm (multiplet, 1+2=3 protons); and 4.9 ppm (multiplet, 1 proton).

Example 7

23 g of sodium were dissolved in 500 ml of absolute ethanol, 174 g of acetoacetic acid tert.-butyl ester were added, 1 g of hydroquinone was added and 104.5 g of 3 - chloro - 3 - methyl - 1 - butene were then added dropwise at 60°C. When the dropwise addition was complete, the mixture was heated to the reflux temperature for a further one hour. It was then allowed to cool and left to stand overnight. The sodium chloride which had precipitated was filtered off and washed with ethanol and the solvent was stripped off from the combined filtrates under reduced pressure. The residue was rendered neutral with ice-cold dilute hydrochloric acid and extracted three times with methylene chloride. The methylene chloride extracts were dried over sodium sulphate, the sodium sulphate was filtered off and the filtrate was concentrated *in vacuo*. The residue was subjected to fractional distillation under a high vacuum. 1,1 - Dimethyl - 2 - propenyl - acetoacetic acid tert.-butyl ester boiled at a boiling point of 62—66°C/0.08 mm Hg. The nuclear magnetic resonance spectrum confirmed the structure:

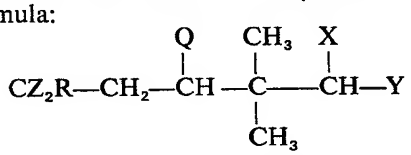
δ ($CDCl_3$): 1.05 ppm (singlet, 9 protons); 1.3 ppm (singlet, 6 protons); 2.2 ppm (singlet, 3 protons); 3.5 ppm (singlet, 1 proton) and 4.9 and 5.9 ppm (multiplet, 2+1=3 protons).

Example 8

113 g of 1,1 - dimethyl - 2 - propenyl - acetoacetic acid tert. - butyl ester were dissolved in 1,000 ml of carbon tetrachloride and 40 g of benzoyl peroxide were added. The mixture was boiled for 8 hours under reflux, 20 g of benzoyl peroxide were added and the mixture was boiled for a further 8 hours. After cooling, it was washed with cold dilute sodium hydroxide solution in order to remove the benzoic acid formed and the organic phase was dried with sodium sulphate and filtered and the solvent was distilled off under reduced pressure. The residue was subjected to fractional distillation under a high vacuum. 1,1 - Dimethyl - 2,4,4,4 - tetra - chloro - butyl - acetoacetic acid tert. - butyl ester boiled at a boiling point of 138—145°C/0.1 mm Hg. Yield: 128 g. The nuclear magnetic resonance spectrum confirmed the structure:

δ (in $CDCl_3$): 1.05 ppm (singlet, 9 protons); 1.3 ppm (singlet, 6 protons); 2.2 ppm (singlet, 3 protons); 3.2 ppm (multiplet, 2 protons); 3.75 ppm (singlet, 1 proton) and 4.8 ppm (multiplet, 1 proton).

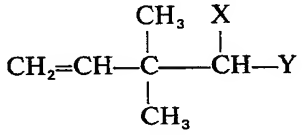
We are aware of the complete specification of Patent No. 1,520,024 which describes and claims a compound of the formula:



wherein X and Y are independently selected from cyano and alkoxycarbonyl containing from 1 to 4 carbon atoms in the alkoxy group, and Q, R and Z are independently selected from chlorine and bromine, provided that Q is always bromine, when either of Z and R is bromine.

In such a compound R and Z may both be chlorine.

As well as the above compounds there is also described and claimed a process for preparing such compounds which comprises reacting a compound of formula:



with a tetrahalomethane of formula CZ_2QR where Q and R are independently selected from chlorine and bromine provided that Q is always bromine, in the presence of a free radical catalyst.

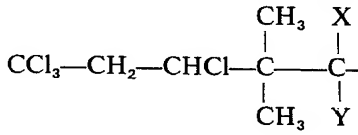
In such a process the tetrahalomethane may be carbon tetrachloride.

It is to be understood that we make no claim to a compound or process as claimed in the complete specification of Patent No. 1,520,024 as defined above.

Subject to the foregoing disclaimer:

WHAT WE CLAIM IS:—

1. The compounds of the general formula



(III)

in which

X and Y, which may be identical or different, each represent CN, the radical —COOR or the radical —COR^1, provided that X and Y do not both represent CN,

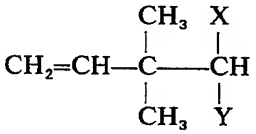
R represents C_1—C_4 alkyl, aralkyl or aryl, and

R^1 represents C_1—C_4 alkyl.

2. Compounds according to claim 1, in which X and Y each represent CN, —$COCH_3$ or a radical —COOR wherein R represents C_1—C_4 alkyl, benzyl or phenyl.

3. Compounds according to claim 2, in which X and Y each represent a radical —COOR wherein R represents methyl, ethyl or tert.-butyl.

4. A process for the preparation of a compound according to claim 1, in which a compound of the general formula



(IV),

in which

X and Y have the meanings stated in claim 1, is reacted with CCl_4 in the presence of a diluent and of a suitable catalyst.

5. A process according to claim 4, in which the catalyst is a peroxide, an azo compound, a transition metal complex or a mixture of a copper(I) salt and a base.

6. A process according to claim 5, in which the catalyst is di - tert. - butyl peroxide, benzoyl peroxide or azo - bis - isobutyronitrile.

7. A process according to claim 4, 5 or 6, in which the diluent is an excess of CCl_4.

8. A process according to any of claims 4 to 7 in which the reaction is effected at from 77° to 150°C.

9. A process for the preparation of a compound according to claim 1, substantially as described in Example 2, 6 or 8.

10. Compounds according to claim 1, whenever prepared by a process according to any of claims 4 to 9.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1980
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.